Box 5. Assessment Scales for Adult Major Depressive Disorder

- Beck Depression Inventory (BDI)
- Patient Health Questionairre-9 (PHQ-9)
- Quick Inventory of Depression Symptomatology (QIDS)

**Notes: The recommendations are based on the evidence-base and clinical consensus. The Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D) can also be used to assess symptoms of depression in major depressive disorder.*

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see pages 2-3.

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 4-9.

The therapeutic objectives of acute treatment are to assure safety, measure response to therapy, provide psychoeducation to patient and circle of care, and to begin the process of symptomatic, syndromal, and functional recovery.

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Assess for:

- Current/prior hypomania/mania, symptoms/episodes*
- Psychiatric and medical comorbidities (e.g., substance-related disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers, notably: psychosis, mixed features, suicidality
- Presence of cognitive dysfunction (e.g., memory complaints; difficulty with concentration, making decisions, and thinking clearly)
- Assess for recurrence vulnerability factors (e.g., symptom severity, age of onset, number of depressive episodes)
- Manual-based psychotherapy (e.g., CBT) or exercise therapy may be an appropriate treatment option for mild depression (e.g., PHQ-9 score 5 through 9). Guided online protocolized psychotherapy may be appropriate where accessible.

**Note: Rule out the possibility of bipolar disorder in individuals presenting with depressive symptoms.*

Level 1 Options for initial treatment:

- Antidepressant Monotherapy trial at adequate dose and evaluate*:
  - Selective serotonin reuptake inhibitor (SSRI)**, serotonin-norepinephrine reuptake inhibitor (SNRI), vortioxetine, dextromethorphan-bupropion
  - Bupropion monotherapy or mirtazapine
- Consider brexanolone in persons with postpartum depression
- In adults with acute suicidal ideation or actions, intranasal esketamine co-administered with a conventional antidepressant can be initiated at any level of treatment.
- If partial response at 2 to 4 weeks, may continue for another 2 to 4 weeks or go to Level 2.

If no response at 4 weeks, ensure dose optimization and go to Level 2.

**Medication response is more pronounced in moderate to severe depression.*

***Consider propensity for drug-drug interactions and differential risk for teratogenicity.*

Initiate combination therapy for individuals with recurrent depression, persistent depressive disorder, and history of trauma. Be vigilant of emergence of hypomanic symptoms.

Level 2 If multiple Level 1 trials are ineffective and/or not well tolerated:

- Evaluate adherence
- Ensure dose optimization of medication used in Level 1.
- Switch to different monotherapy agent from different or same class (SSRI, SNRI, bupropion, or mirtazapine).
- Combine existing monotherapy with:
  - Evidence-based psychotherapy (e.g., CBT, IPT)
  - Second-generation antipsychotic FDA-approved for augmentation therapy for major depressive disorder (MDD) (i.e., aripiprazole or brexpiprazole or cariprazine; quetiapine is Level 3 due to tolerability concerns)
  - Intranasal esketamine or intravenous racemic ketamine. In the case of intranasal esketamine, co-administration with a separate antidepressant.
  - An antidepressant (avoid SSRI and SSRI/SNRI combinations)
- Accelerated TMS protocol. Consider MRI-guided TMS where accessible.

Note: FDA-approved adjunctive agents for MDD are select atypical antipsychotics. Preliminary evidence evaluating comparative effectiveness of adjunctive antidepressant versus adjunctive atypical antipsychotic medications indicates superior efficacy for adjunctive antipsychotics and superior tolerability for adjunctive antidepressants.

Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- Evaluate adherence
- Seek psychiatric consultation
- (SSRI or SNRI) + quetiapine (tolerability concerns)
- (SSRI or SNRI) + (lithium or T3)
- (SSRI or SNRI) + (L-Methylfolate or S-adenosylomethionine)
- Tricyclic antidepressant (TCA)
- Monoamine oxidase inhibitor (MAOI)
- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)*

**Note: Most evidence for TMS is in the acute treatment.*

Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:

- Re-evaluate diagnosis if patient has failed to respond to 2 or more treatments
- Monoamine oxidase inhibitor (MAOI) augmentation (AVOID CONTRAINDICATED COMBINATIONS)
- Triple drug combination (little evidence exists supporting or refuting this strategy)
  - (SSRI or SNRI) + mirtazapine + bupropion
  - (SSRI or SNRI) + mirtazapine + lithium*
  - (SSRI or SNRI) + bupropion + second generation antipsychotic (SGA)
- Other neuromodulatory approaches [e.g., vagus nerve stimulation (VNS)]

**Note: Caution should be used when prescribing lithium due to increased risk to the fetus with use during pregnancy (i.e., Ebstein's anomaly).*

Box 6. Assessment Scales for Adult Major Depressive Disorder with Mixed Features

- Beck Depression Inventory
- Clinical Global Impression (CGI) Scale
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Patient Health Questionairre-9 (PHQ-9)
- Quick Inventory of Depression Symptomatology (QIDS)
- Young Mania Rating Scale (YMRS)

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see pages 2-3.

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 4-9.

Mixed features are subsyndromal hypomanic features defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision (DSM-5TR).

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g., substance use disorders, anxiety disorders, obesity, diabetes)

Level 1 Initial Treatment:

- Minimal evidence for treating major depressive order (MDD) with mixed features specifier
- Discuss treatment option, including evidence-based psychotherapy [Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), Behavioral Activation]
- Consider FDA-approved second-generation antipsychotic (SGA; lurasidone, lumateperone, cariprazine)** for augmentation in MDD or mood stabilizer (e.g., lithium*)
- Antidepressant monotherapy 4 to 8-week trial at adequate dose and evaluate
  - Selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine
  - Bupropion (if tolerability concerns) or mirtazapine

Note: Antidepressant monotherapy in MDD with subsyndromal hypomania may be associated with a higher rate of suboptimal therapeutic outcomes when compared to MDD without subsyndromal hypomania.

- For all Level 1 treatments, if partial response at 4 weeks, may continue for another 2 to 4 weeks or go to Level 2.
- For all Level 1 treatments, if no response at 4 weeks, ensure dose optimization and go to Level 2.

Level 2 If multiple Level 1 trials are ineffective and/or not well tolerated:

- Reassess for hypomania/mania
- Ensure dose optimization of medication used in Level 1
- Switch to lurasidone or lumeteperone monotherapy or adjunct

Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- Alternative adjunctive SGA or lithium or lamotrigine
- Consider electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS; consider accelerated TMS protocol)
- Alternative antidepressants, including tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or first-generation antipsychotic (FGA)**

Notes:

**Caution should be used when prescribing lithium, lamotrigine, divalproex or carbamazepine to women of reproductive age due to increased risks to the fetus with use during pregnancy, including neural tube and other birth defects. Please see Florida Best Practice Recommendations for Women of Reproductive Age with Serious Mental Illness and Comorbid Substance Use Disorders and online guideline on the Pharmacological Treatment of Mood Disorders During Pregnancy available at https://floridabhcenter.org.*

***Side-effect concerns with these agents include weight gain, metabolic syndrome, and extrapyramidal symptoms (EPS). Side-effects warrant vigilance and close monitoring on the part of the clinician.*

Treatment of Major Depressive Disorder with Psychotic Features

Box 7. Assessment Scales for Adult Major Depressive Disorder with Psychotic Features

- Beck Depression Inventory
- Brief Psychiatric Rating Scale
- Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS)
- Hamilton Rating scale for Depression (HAM-D)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Positive and Negative Syndrome Scale (PANSS)

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see pages 2-3.

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 4-9.

Psychotic features are the presence of delusions and/or hallucinations as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision (DSM-5TR). Psychotic features may be mood-congruent, where the content of all delusions and/or hallucinations are consistent with typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment, or mood-incongruent, where the content of the delusions and/or hallucinations either does not involve these typical depressive themes or is a mixture of mood-congruent and mood-incongruent themes.

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Assess for:

- Prior history of hypomania/mania
- If MDD with psychosis presents post-partum, evaluate for bipolar disorder.
- Psychiatric and medical comorbidities (e.g., substance use disorders, anxiety disorders, obesity, diabetes)

Level 1 Options for initial treatment:

- Treatment with Level 1 antidepressant for major depressive disorder without psychotic features. Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) or vortioxetine + second generation antipsychotic (SGA)*
- Electroconvulsive therapy (ECT) (if patient safety is an immediate concern)
- Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are not recommended as a first-line modality.

**Consider extrapyramidal symptoms (EPS) risk and metabolic concerns, including weight gain.*

Level 2 If multiple Level 1 trials are ineffective and/or not well tolerated:

- Alternative antidepressant + SGA combination
- ECT

Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- Re-evaluate diagnosis
- Other antidepressant combinations with SGA
- Other antidepressant combinations with first generation antipsychotic (FGA)
- ECT (if not attempted earlier)

Summary: Treatment of Major Depressive Disorder

Roger S. McIntyre, M.D., FRCPC
Professor of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada
Board Chair, Depression and Bipolar Support Alliance (DBSA) Board of Directors, Chicago, Illinois, USA

Introduction

It is amply documented that major depressive disorder (MDD) is a prevalent, early age at onset, severe disorder with high rates of non-recovery, recurrence and chronicity. The COVID-19 pandemic has resulted in an increase in the number of persons across the USA and globally affected by MDD and related disorders (e.g., anxiety disorders). The foregoing composite of MDD alongside the national opioid epidemic and increased reporting of suicidality, especially amongst younger populations, has resulted in a consensus position that the USA and many other countries around the world are experiencing a mental health crisis.

Busy practitioners are highly familiar with the overlap of MDD with other mental disorders as well as disparate medical conditions. The vulnerability to medical conditions amongst persons living with mood disorders was further instantiated by observations of persons living with MDD are at greater risk of contracting COVID-19, experiencing complications due to COVID-19 requiring hospitalization as well as mortality. Moreover, the morbidity of MDD is amplified further by the existence of comorbid conditions and results in an increase in health service utilization and costs.

Accumulated research results during the past decade indicates that the majority of adults with MDD are either undiagnosed or delayed in receiving the diagnosis. For persons with access to healthcare settings the majority are not prescribed evidence-based strategies, and for those who are, discontinuation occurs for most persons within a few months. The foregoing "knowledge-implementation" gap represents a robust modifiable deficiency in managing adults with MDD. In addition, most persons with MDD are not receiving "next-step" treatments if the first-line treatment proves to be inadequate resulting in a sizable proportion of persons with MDD impaired by the illness unnecessarily.

The diagnosis of MDD remains a clinical endeavor and the selection of antidepressant treatment is informed by "deep in vivo" clinical characterization of the patient. Digital psychiatry holds tremendous promise for the future from the point of view of ecological momentary assessment (EMA), passive ambient digital fingerprinting of the illness, illness self-management as well as multidisciplinary case management and evaluation for suicide risk. Moreover, virtual healthcare across different media skyrocketed during the pandemic and is undoubtedly remaining a significant access point for persons living with MDD as well as a framework to provide protocolized psychotherapies. As with pharmacogenomics, however, the digital revolution (with the exception of telehealth) at point-of-care implementation remains a future aspiration rather than routine practice today.

During the past four years, the FDA has approved for MDD several new treatment approaches including by not limited to intranasal esketamine (for treatment-resistant depression and depression with suicidality), combination dextromethorphan-bupropion, the first rapid-acting oral NMDA antagonist and sigma 1 agonist, the dopamine D2/D3 partial agonist atypical antipsychotic cariprazine as well as cleared MRI-guided accelerated transcranial stimulation (the first time the FDA has cleared and/or approved radiology as a component of the treatment of a persons with a mental disorder). These developments along with refinement of protocolized psychotherapies that are accessible via telehealth provides hope for persons living with MDD that genuinely innovative strategies are appearing.

Moreover, later in 2023 it is anticipated that the FDA will decide whether it will approve the first ever GABA-ergic antidepressant that is taken "when needed" for a brief duration (i.e., two weeks) representing a tectonic plate shift in the management of this chronic disorder.

As we anticipate approval of innovative new approaches narrowing the implementation gap, fidelity to evidence-based approaches, measurement-based care and guideline-informed treatments remain accessible and powerful approaches. Clinicians are encouraged to be sensitive to inequities in the healthcare system as a function of race, ethnicity, gender identification, sexual orientation and/or economic position when assessing and providing care as an additional area for improvement in managing persons living MDD.

Principles of Treatment

Similar to the 2019-2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults, the emphasis for the 2023 guidelines is the emphasis on full functional recovery and integration as a priority therapeutic objective in MDD. Towards this overarching and patient-desired aim, it is essential that clinicians consider self-rating instruments when screening for MDD. It is also essential that once the clinical diagnosis of MDD has been established that therapeutic objectives include full symptom mitigation and consensually agreed upon therapeutic objectives in collaboration with patients. Available evidence also indicates that individuals with MDD who function at a higher level, despite being depressed, are more likely to respond and remit with antidepressant therapy. Along with underscoring the complex interrelationship between symptoms and function in MDD, the improved symptomatic outcomes in higher functioning adults with MDD provides the impetus for simultaneously targeting symptoms and functioning in patients with MDD.

Along with careful attention to the presence of depressive symptoms, the relatively high rates of medical and mental disorder comorbidity in the MDD population provides the basis for careful attention to preventing and, when present, treating comorbidity in MDD populations. Commonly encountered comorbidities (e.g., anxiety disorder, substance use disorders, attention deficit hyperactivity disorder, eating disorders), as well as medical disorders (e.g., cardiovascular disease, obesity, diabetes mellitus) should be part of routine assessment of any adult with MDD. Moreover, as with all patients, assessing for imminent risk of suicide is critical. Unfortunately, psychiatry is unable to predict suicide in ways that are robust, evidence-based and clinically applicable. The hope is that the future, perhaps through artificial intelligence machine-learning, we position clinicians to better predict lethal self-harm.

For many individuals presenting with depression of mild severity, manual-based psychotherapy may be a preferred option. Moreover, exercise therapy has also demonstrated symptom mitigating effects in individuals with depressive episodes of milder severity. For others presenting with depression of moderate to severe depressive episodes as part of MDD, pharmacotherapy should certainly be considered. In many cases, manual-based psychotherapy can also be an alternative and/or adjunctive treatment. The current evidence base indicates that for adults with treatment-resistant MDD, manual-based psychotherapy is most effective when combined with pharmacotherapy. Moreover, combination pharmacotherapy-manual based psychotherapy approaches are recommended for persons with persistent depressive disorder, MDD with select comorbidities (e.g., obsessive compulsive disorder) and situations where patients report histories of childhood trauma and/or manifest maladaptive personality traits.

Practitioners very frequently encounter persons living with MDD who exhibit inadequate response to first-line antidepressant treatments. Treatment-resistant depression (TRD) does not have a consensus definition and/or been externally validated by a biomarker. The absence of a validated biomarker has resulted in a range of prevalence estimates from approximately

30-60%. For adults presenting with inadequate response to first-line treatments, FDA-approved second-generation atypical antipsychotics should be considered ahead of adjunctive antidepressants. Available evidence does suggest that although combining antidepressants together can be effective and well-tolerated, the rigor of that data is inferior to data with atypical antipsychotics. For persons not tolerating the first-line treatment, switching is recommended; if the first-line treatment is sufficiently tolerated there are advantages to adjunctive strategies if patients prefer that approach with some suggestion of superiority with adjunctive atypical agents when compared to switching to antidepressant monotherapy. For persons with TRD, ECT, rTMS and esketamine co-initiated with an antidepressant can be considered as well as off-label intravenous racemic ketamine. Available evidence suggests that esketamine may be relatively more efficacious than some second-generation antipsychotics in adults with TRD.

Major Depressive Disorder Without Mixed Features

The DSM-5 introduced mixed features specifier in the manual published in 2013. Mixed features refers to subthreshold hypomanic symptoms occurring during a depressive episode in an individual with MDD. The panel was of the view that the hazards posed by mixed features (e.g., a more complex illness presentation, higher rates of comorbidity, suicidality) as well as diminished response to conventional antidepressants warrants assessment as to the presence or absence of mixed features. In an adult who is presenting MDD without mixed features, clinicians are encouraged to select and sequence treatments according to the ***2023–2024 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults***.

Major Depressive Disorder with Mixed Features

For patients presenting with MDD and mixed features, the panel was of the view that it is important to consider the possibility that the identified patient may possibly have bipolar disorder. Longitudinal studies indicate that the majority of individuals with MDD and mixed features exhibit phenotypic stability across time (i.e., they retain the diagnosis of MDD). Notwithstanding, the relative risk for bipolar disorder in adults with MDD and mixed features is increased relative to the general population. Conventional antidepressants can and should be considered with careful attention for any amplification and/or new onset hypomanic symptoms. Symptom intensification manifests in many ways including, but not limited to, anxiety, agitation, irritability, dysphoria and sleep disruption. Preliminary evidence suggests that for some adults with MDD with mixed features, second-generation antipsychotics may not only be efficacious but may also be better tolerated in this particular population. As per the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults, the panel agreed that despite the lack of rigorous evidence, other agents with mood stabilizing properties (e.g., lithium, lamotrigine) may also be considered in MDD with mixed features as an adjunct to antidepressants or perhaps in some cases, as a treatment alternative.

Major Depressive Disorder with Psychosis

There was no substantive change in the panel's recommendation in treatment for MDD with psychosis. MDD with psychosis affects at least 20% of individuals with MDD. Results from a recently completed randomized control trial provide results that comport with clinical impression that the combination of a conventional antidepressant and antipsychotic is the preferred, acute, and recurrence-prevention treatment option when compared to conventional antidepressant monotherapy. Indeed, electroconvulsive therapy is an alternative treatment option for MDD with psychosis; antidepressant monotherapy as well as manual-based psychotherapy as stand-alone treatment are not recommended.

Maintenance Treatment in Major Depressive Disorder

Evidence indicates that the majority of individuals with MDD are at risk of recurrence. Furthermore, episode frequency is a powerful predictor of future episodes. Delineating which patients should be considered for longer-term therapy is informed by identifying recurrence vulnerability factors (e.g., number of prior episodes, residual symptoms, cognitive symptoms, comorbidity, and stressors). Clinicians are encouraged to consider long-tern tolerability and safety concerns (e.g., weight gain, glucose homeostatic disturbances) when selecting antidepressants acutely. Evidence also indicates that manual-based psychotherapy as well as mindfulness-based psychotherapeutic approaches can be helpful adjunctive and/or alternative treatment strategies during the maintenance treatment of MDD in individuals who have acutely responded to antidepressant monotherapy. The overarching therapeutic objective of maintenance treatment in MDD is to assist patients in full functional recovery in achieving consensually agreed upon PROs. A point of emphasis is that psychosocial treatments, including protocolized psychotherapies, should be considered as maintenance treatments in persons with MDD.

References:

1. Ceban F, Nogo D, Carvalho IP, et al. Association Between Mood Disorders and Risk of COVID-19 Infection, Hospitalization, and Death: A Systematic Review and Meta-analysis. JAMA Psychiatry 2021;78(10):1079–91.
2. Maj M, Stein DJ, Parker G, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry 2020;19(3):269–93.
3. Kessler RC, Kazdin AE, Aguilar-Gaxiola S, et al. Patterns and correlates of patient-reported helpfulness of treatment for common mental and substance use disorders in the WHO World Mental Health Surveys. World Psychiatry 2022;21(2):272–86.
4. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry 2021;178(5):383–99.